

Remarks

Amendments

The specification has been amended to update the priority claim. The specification has also been amended to delete Table 2 from page 35. Table 2 is present as Figure 6. The specification has been amended to add a description of Table 2. No new matter is added by these amendments and applicants respectfully request their entry. A supplemental patent application data sheet is filed herewith.

Claims 1, 6, 11, 13, and 15 have been amended to recite “only” *in vivo*. The addition of the term “only” does not change scope or meaning of claims. Polynucleotides can be expressed by microbes *in vivo* only and not *in vitro*. The methods of the invention can identify polynucleotides that are expressed by a microbe only when the microbe is in a host (*in vivo*). Support for the amendments can be found in the specification at, *inter alia*, page 8, lines 14-15.

Claims 1, 6, 11, 13, and 15 have been amended to recite “isolating” and/or “isolated.” Support for the amendment can be found in the specification at, *inter alia*, page 10, lines 9-10. This is not a narrowing amendment.

Claims 1, 11, 13, and 15 have been amended to recite that clones that bind to unabsorbed antibodies are isolated from the expression library. Support for this clarifying amendment can be found in the specification at, *inter alia*, page 13, line 16 through page 14, line 6; page 31, line 7 through page 33, line 3.

Claim 7 has been amended to recite that the “antibodies of step (a) are obtained from sera from one or more hosts infected with, or previously infected with the microbe.” Support for the amendment can be found in the specification at, *inter alia*, page 10, line 20 through page 11, line 3.

Claim 10 has been amended to correct its dependency and antecedent basis.

Amendments to the claims are made without prejudice or disclaimer, and do not constitute amendments to overcome any prior art or other statutory rejections. The amendments are fully supported by the specification as filed and thus do not introduce new matter. Additionally, these amendments are not and should not be construed as admissions regarding the patentability of the claimed subject matter. Applicants reserve

the right to pursue the subject matter of previously presented claims in this or in any other appropriate continuation, continuation in part, or divisional patent application. Applicants expressly reserve the right to seek broader claims in this or any other appropriate continuation, continuation in part, or divisional application. Accordingly, Applicants respectfully request the entry of the amendments presented herein.

Objections to the Drawings and Specification

A description of Figure 6 has been added to the specification. Additionally, correction of the priority information has been made. Applicants respectfully request withdrawal of the objections to the drawings and specification.

Rejection of Claims 1-17 Under 35 U.S.C. §112, first paragraph

Claims 1-17 stand rejected under 35 U.S.C. §112, first paragraph as allegedly lacking written description. Applicants respectfully traverse the rejection.

An adequate written description can be demonstrated by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the invention. *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323 (Fed. Cir. 2000). A determination as to whether one of skill in the art would recognize that the applicant was in possession of the claimed invention.

The instant claims recite methods for identifying and isolating polynucleotides that are expressed only during *in vivo* growth of a microbe or pathogen. That is, the methods can be used to, *e.g.*, identify polynucleotides that are expressed by a microbe while it is living or growing within a host (*in vivo*), but that are not expressed by the microbe while it is living or growing *in vitro* (*e.g.*, in a laboratory). This is important because it is unlikely that all regulated virulence determinants of a microbe can be identified *in vitro* because it is technically impossible to determine and mimic all of the complex and changing environmental stimuli that occur at the site of an infection. *See* specification, page 1. Advantageously, the methods of the invention do not require the use of animal models of infection.

Therefore, the invention provides methods of identifying polypeptides of a microbe that are expressed only *in vivo*, that is, while the microbe is present in a host. The Office asserts that “[w]ith the exception of SEQ ID NOs:1-8 and *Actinobacillus actinomycetemcomitans* antigens as disclosed by the specification, the skilled artisan

cannot envision the method of claims 1-5.” The Office appears to imply that all polynucleotides that could be identified using the methodology of the invention must be disclosed in the specification. Of course, that would render the valuable methodology of the invention useless. Instead, the proper inquiry is whether one of skill in the art would recognize that the applicants were in possession of the claimed methods.

The Office asserts that specification does not include any structural information regarding the antibodies or antigens used in the claimed methods and states that “claims drawn to or utilizing antibodies and antigens require that the antibody or antigen is taught due to the nature of antigen-antibody binding and the required specificity for useful products.” The Office relies on cases relating to written description of specific DNA molecules (*Fiers v. Revel*; *Amgen Inc. v. Chugai Pharmaceutical Co.*; *Fiddes v. Baird*). The instant case, however, claims methods of identifying polynucleotides and the polypeptides encoded by the polynucleotides.

One of skill in the art would recognize that the applicants were in possession of the claimed methods and the compositions required to practice the claimed methods because, *inter alia*, the methods and required compositions are described in detail in the specification and working examples of the methods are provided. Claim 1, step (a) recites: “adsorbing antibodies against antigens that are expressed by the microbe *in vivo* and *in vitro* with cells or cellular extracts of the microbe that have been grown *in vitro*.”

The specification teaches that:

A sample of antibodies against antigens that are expressed by a microbe *in vivo* and *in vitro* is collected. The sample can comprise the serum of a host or hosts infected with or previously infected with the microbe.

See specification, page 10, lines 19-21. One of skill in the art, given the specification, would understand that applicants were in possession of the claimed methods because the specification teaches that “antibodies against antigens that are expressed by the microbe *in vivo* and *in vitro*” can be, *e.g.*, the serum of a host or hosts infected with or previously infected with the microbe.

Furthermore, the specification teaches that:

Preferably, a sample containing antibodies against antigens that are expressed by the microbe *in vivo* and *in vitro*, such as a serum sample of an infected host, are contacted with *in vitro* grown whole cells, cell

extracts or both of the microbe, or whole cells, extracts of whole cells, or both of cells that are infected with the microbe of interest, *e.g.* a prokaryotic or eukaryotic cell infected with a virus or parasite.

See specification, page 12, lines 19-21. Therefore, one of skill in the art, given the specification, would understand that applicants were in possession of the claimed methods because the specification teaches that “cells or cellular extracts of the microbe that have been grown *in vitro*” can be, *e.g.*, *in vitro* grown whole cells, cell extracts or both of the microbe, or whole cells, extracts of whole cells, or both of cells that are infected with the microbe of interest. Furthermore, working examples that demonstrate the actual reduction to practice of the claimed methods and that detail the types of compositions that can be used to perform the claimed methods are shown in Examples 1-4.

The Office furthermore asserts that:

In addition, the limitations in claims 4, 10, and 17 regarding the animals and the limitations in claims 8-9 regarding the pathogens equate to a laundry list of potential animals and pathogens. A lack of written description also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. *See, e.g., Fujikawa v. Wattanasin* 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a “laundry list” disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not ‘reasonably lead’ those in the art to any particular species.).”

The issue in *Fujikawa* was whether a particular sub-genus of compounds were disclosed in the specification, which disclosed a great number of species of compounds. The court stated that “[c]learly, however, just because a moiety is listed as one possible choice for one position does not mean there is *ipsis verbis* support for every species and sub-species that chooses that moiety. Were this the case, a “laundry list” disclosure of every possible moiety for every possible position would constitute a written description of every species in the genus. This cannot be because such a disclosure would not “reasonably lead” those skilled in the art to any particular species.” *Id.*

Therefore, the court found that that a laundry list of a large genus of compounds did not, in this particular case, provide written description for a certain sub-genus of the

compounds. The instant invention, however, is drawn to methods of identifying polynucleotides of microbes that are expressed only *in vivo*. The methods can be used to isolate polynucleotides of a multitude of microbes that are expressed when the microbes are present in a multitude of hosts. The Office has not demonstrated any reason why one of skill in the art would not believe that the applicants were in possession of methods that can isolate polynucleotides from microbes that are expressed only *in vivo* in hosts, especially since the applications actually reduced the claimed methods to practice in detailed working examples.

The Office recognizes that the specification provides working examples of the methods of the invention, but asserts that the specification fails to teach a single example of the methods of claim 6 or 11-17. These methods however, are clearly described in the specification at, *inter alia*, page 11, lines 4-18; page 14 line 16 through page 15, line 17. Furthermore, a working example of the method of claim 6 is indeed described at Example 4. The Office has not provided cogent reasoning as to why one of skill in the art would not recognize that the applicants were in possession of the claimed methods.

Therefore, one of skill in the art, given the specification would recognize that applications were in possession of the claimed methods because the specification describes the methods in detail and describes the compositions that are necessary to use the methods. The specification even provides working examples of the use of the methods of the invention to identify polynucleotides of *Actinobacillus actinomycetemcomitans* that are expressed only *in vivo*. Therefore, the specification provides adequate written description and applicants respectfully request withdrawal of the rejection.

Rejection of Claims 8-9 Under 35 U.S.C. §112, second paragraph

Claims 8-9 stand rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite. Applicants respectfully traverse the rejection.

The test for definiteness is whether one of skill in the art would understand what is claimed when the claims are read in light of the specification. *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1576 (Fed. Cir. 1986). The Office asserts that the term “microbe” is not definite because the specification “does not clearly redefine the term.” The specification, however, states that:

The microbe or pathogen can be any kind of a bacterium, a virus, a parasite, a prion, or a fungus.

See page 11, lines 22-23. The specification most certainly clearly and explicitly defines a microbe as a bacterium, a virus, a parasite, a prion, or a fungus. As such the claim is definite. Applicants respectfully request withdrawal of the rejection.

Rejection of Claim 7 Under 35 U.S.C. §112, second paragraph

Claim 7 stands rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite. Applicants respectfully traverse the rejection.

Claim 7 has been amended to recite that the “antibodies of step (a) are obtained from sera from one or more hosts infected with, or previously infected with the microbe.” The claim is definite and applicants respectfully request withdrawal of the rejection.

Rejection of Claim 10 Under 35 U.S.C. §112, second paragraph

Claim 10 stands rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite. Applicants respectfully traverse the rejection.

Claim 10 has been amended to correct its dependency. The claim is definite. Applicants respectfully request withdrawal of the rejection.

Rejection of Claims 1-10 Under 35 U.S.C. §112, second paragraph

Claims 1-10 stand rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite. Applicants respectfully traverse the rejection.

The Office asserts that the method of independent claim 1 has three method steps, but it is not clear if the wherein clause (*i.e.*, wherein a polynucleotide of the microbe that is expressed *in vivo* is isolated) is a separate method step or a product by process limitation regarding the reagent utilized in method step (c). Step (c) of claim 1 has been amended to recite “and isolating clones from the expression library that bind to the antibodies of step (b)” to clarify that polynucleotides of the microbe (present in the isolated clones) is isolated. That is, by isolating the clones that bind to the antibodies of step (b) a polynucleotide that is expressed only *in vivo* by the microbe is isolated.

The Office asserts that it is unclear if method steps are required by the claims or not and points to the following claim phrases as allegedly lacking positive method steps:

- “antigens that are expressed by the microbe *in vivo* and *in vitro*”
- “cells or cellular extracts of the microbe that have been grown *in vitro*”
- “polynucleotide of the microbe that is expressed *in vivo* is isolated and identified”

One positive method step of claim 1 is: “adsorbing antibodies against antigens that are expressed by the microbe *in vivo* and *in vitro* with cells or cellular extracts of the microbe that have been grown *in vitro*.” Adsorbing antibodies against certain antigens is clearly a positive method step. The specification teaches that antibodies against antigens that are expressed by the microbe *in vivo* and *in vitro* and teaches that:

A sample of antibodies against antigens that are expressed by a microbe *in vivo* and *in vitro* is collected. The sample can comprise the serum of a host or hosts infected with or previously infected with the microbe.

See specification, page 10, lines 19-21 and working Example 1. One of skill in the art, given the specification, would understand that “antibodies against antigens that are expressed by the microbe *in vivo* and *in vitro*” can be, *e.g.*, the serum of a host or hosts infected with or previously infected with the microbe. Therefore, the first positive method step and compositions required to perform the step would be understood by one of skill in the art given the specification.

Furthermore, the specification teaches that:

Preferably, a sample containing antibodies against antigens that are expressed by the microbe *in vivo* and *in vitro*, such as a serum sample of an infected host, are contacted with *in vitro* grown whole cells, cell extracts or both of the microbe, or whole cells, extracts of whole cells, or both of cells that are infected with the microbe of interest, *e.g.* a prokaryotic or eukaryotic cell infected with a virus or parasite.

See specification, page 12, lines 19-21 and working Example 1. Therefore, one of skill in the art, given the specification, would understand that “cells or cellular extracts of the microbe that have been grown *in vitro*” can be, *e.g.*, *in vitro* grown whole cells, cell extracts or both of the microbe, or whole cells, extracts of whole cells, or both of cells that are infected with the microbe of interest.

Another positive method step is “isolating unadsorbed antibodies.” One of skill in the art would understand this step given the specification. See, *e.g.*, page 12, line 23

through page 13, line 8; and working Example 1, which demonstrates the isolation of unadsorbed antibodies.

Another positive method step is “probing an expression library of the microbe’s DNA or RNA with the antibodies of step (b).” One of skill in the art is familiar with probing expression libraries with antibodies. Furthermore, the specification describes such procedures in detail. See page 13, line 12 through page 13, line 6, and working Example 2. Clones from the expression library that bind with the antibodies of step (b) (*i.e.*, unadsorbed antibodies) are isolated thereby isolating a polynucleotide of the microbe that is expressed only *in vivo*. Reactive clones isolated by probing the expression library can be characterized by conventional analysis to identify a polynucleotide of a microbe that is expressed only *in vivo*. See page 14, lines 1-15 and working Example 3.

The Office appears to assert that the specified phrases represent some sort of “product-by-process” limitations wherein positive method steps must be recited. A product-by-process claim is a product claim that defines the claimed product in terms of the process by which it is made. See MPEP § 2173.05(p). These types of claims are generally considered proper. *Id.* The instant claims are drawn to methods and are therefore not product-by-process claims. As such, the Office’s reference to product-by-process claims is unclear. As pointed out above, the method claims of the invention recite proper positive steps using well-defined compositions and reagents.

The Office asserts that “[i]f the method of independent claim 1 requires the antigens to be expressed *in vivo* and *in vitro*, cells or cellular extracts to be grown *in vitro*, polynucleotides expressed *in vivo*, and/or a polynucleotide to be isolated and identified, applicants are requested to provide positive method steps regarding these limitations to the claims.” As described above each of these limitations is clear such that one of skill in the art would understand what is claimed when the claims are read in light of the specification. Applicants respectfully request withdrawal of the rejection.

Rejection of Claims 11-12 Under 35 U.S.C. §112, second paragraph

Claims 11-12 stand rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite. Applicants respectfully traverse the rejection.

The Office asserts that it is unclear if method steps are required by the claims or not and points to the following claim phrases as allegedly lacking positive method steps:

- “cells or cellular extracts of the microbe that have been grown *in vitro*”
- “polynucleotides of the microbe that are expressed *in vivo* are identified.”

Claim 11 recites a positive method step of:

adsorbing a first sera sample from one or more hosts infected with or previously infected with the microbe, with cells or cellular extracts of the microbe that have been grown *in vitro*, wherein each host is in about the same stage of the infection.

One of skill in the art would understand the positive method step of adsorbing a sera sample with cells or cellular extracts of the microbe that have been grown *in vitro*. The specification teaches that:

Preferably, a sample containing antibodies against antigens that are expressed by the microbe *in vivo* and *in vitro*, such as a serum sample of an infected host, are contacted with *in vitro* grown whole cells, cell extracts or both of the microbe, or whole cells, extracts of whole cells, or both of cells that are infected with the microbe of interest, *e.g.* a prokaryotic or eukaryotic cell infected with a virus or parasite.

See specification, page 12, lines 19-21 and working Example 1. Therefore, one of skill in the art, given the specification, would understand that “cells or cellular extracts of the microbe that have been grown *in vitro*” can be, *e.g.*, *in vitro* grown whole cells, cell extracts or both of the microbe, or whole cells, extracts of whole cells, or both of cells that are infected with the microbe of interest. Furthermore, the specification discusses this positive method step at, *inter alia*, page 12, line 14 through page 13, line 8 and working example 1.

Another positive method step is “probing a first expression library of the microbe with the unadsorbed antibodies from the first serum sample and isolating clones from the first expression library that bind to antibodies from the first serum sample, and probing a second expression library with the unadsorbed antibodies from the second serum sample and isolating clones from the second expression library that bind to antibodies from the second serum sample, wherein polynucleotides of the microbe that are expressed only *in*

vivo are isolated for the first and second serum sample” One of skill in the art is familiar with probing expression libraries with antibodies. Furthermore, the specification describes such procedures in detail. *See* page 13, line 12 through page 13, line 6, and working Example 2. Clones from the expression library that bind with the unadsorbed antibodies are isolated thereby isolating a polynucleotide of the microbe that is expressed only *in vivo*. Reactive clones isolated by probing the expression library can be characterized by conventional analysis to identify a polynucleotide of a microbe that is expressed only *in vivo*. *See* page 14, lines 1-15 and working Example 3.

The Office asserts that “[i]f the method of independent claim 11 requires the cells or cellular extracts to be grown *in vitro* or the polynucleotide to be expressed *in vivo*, applicants are requested to provide positive method steps regarding these limitations into the claims.” As described above each of these limitations are clear such that one of skill in the art would understand what is claimed when the claims are read in light of the specification. Applicants respectfully request withdrawal of the rejection.

Rejection of Claims 13-14 Under 35 U.S.C. §112, second paragraph

Claims 13-14 stand rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite. Applicants respectfully traverse the rejection.

The Office asserts that it is unclear if method steps are required by the claims or not and points to the following claim phrases as allegedly lacking positive method steps:

- “cells or cellular extracts of the microbe that have been grown *in vitro*”
- “route of infection” for how the microbe enters the host
- “polynucleotides of the microbe that are expressed *in vivo*.”

Claim 13 recites a positive method step of:

adsorbing a first sera sample from one or more hosts infected with or previously infected with the microbe, with cells or cellular extracts of the microbe that have been grown *in vitro*, wherein each host has been infected by about the same route of infection.

One of skill in the art would understand the step of adsorbing a sera sample with cells or cellular extracts of the microbe that have been grown *in vitro*. The specification teaches that:

Preferably, a sample containing antibodies against antigens that are expressed by the microbe *in vivo* and *in vitro*, such as a serum sample of an infected host, are contacted with *in vitro* grown whole cells, cell extracts or both of the microbe, or whole cells, extracts of whole cells, or both of cells that are infected with the microbe of interest, *e.g.* a prokaryotic or eukaryotic cell infected with a virus or parasite.

See specification, page 12, lines 19-21 and working Example 1. Therefore, one of skill in the art, given the specification, would understand that “cells or cellular extracts of the microbe that have been grown *in vitro*” can be, *e.g.*, *in vitro* grown whole cells, cell extracts or both of the microbe, or whole cells, extracts of whole cells, or both of cells that are infected with the microbe of interest. Furthermore, the specification discusses this positive method step at, *inter alia*, page 12, line 14 through page 13, line 8 and working Example 1.

Claim 13 additionally recites: “wherein each host has been infected by about the same route of infection.” The specification teaches that:

Also, certain pathogens can infect humans by more than one route (*e.g.*, via a wound, gastrointestinal tract, respiratory tract, or skin); in such cases, selective pooling of serum from patients infected by various routes may enable the identification of route-specific *in vivo* induced proteins. In cases where different clonal variants or strains of the microbe cause disease, selective pooling of serum from patients infected by various clonal variants or strains can enable the study of the pathogenesis of each variant or strain.

A host may be any kind of animal. For example, hosts can comprise humans, baboons, chimpanzees, macaques, cattle, sheep, pigs, horses, goats, dogs, cats, rabbits, guinea pigs, rats, mice, chickens, ducks, fish, and shellfish.

See page 11, lines 13-21. Therefore, one of skill in the art would clearly understand that one step of the claims includes adsorbing a first sera sample from one or more hosts infected with or previously infected with the microbe, with cells or cellular extracts of the microbe that have been grown *in vitro*, wherein each host has been infected by about the same route of infection.

Another positive method step is “probing a first expression library of the microbe with the unadsorbed antibodies from the first serum sample and isolating clones from the first expression library that bind to antibodies from the first serum sample, and probing a second expression library with the unadsorbed antibodies from the second serum sample and isolating clones from the second expression library that bind to antibodies from the second serum sample, wherein polynucleotides of the microbe that are expressed *in vivo* are isolated for the first and second serum sample.” One of skill in the art is familiar with probing expression libraries with antibodies. Furthermore, the specification describes such procedures in detail. *See* page 13, line 12 through page 13, line 6, and working Example 2. Clones from the expression library that bind with the unadsorbed antibodies are isolated thereby isolating a polynucleotide of the microbe that is expressed only *in vivo*. Reactive clones isolated by probing the expression library can be characterized by conventional analysis to identify a polynucleotide of a microbe that is expressed only *in vivo*. *See* page 14, lines 1-15 and working Example 3.

The Office asserts that “[i]f the method of independent claim 13 requires the cells or cellular extracts to be grown *in vitro*, administration of microbes via the same or different route of administration, or the polynucleotide to be expressed *in vivo*, applicants are requested to provide positive method steps regarding these limitations into the claims.” As described above each of these limitations are clear such that one of skill in the art would understand what is claimed when the claims are read in light of the specification. Applicants respectfully request withdrawal of the rejection.

Rejection of Claim 15-17 Under 35 U.S.C. §112, second paragraph

Claim 15-17 stand rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite. Applicants respectfully traverse the rejection.

The Office asserts that it is unclear if method steps are required by the claims or not and points to the following claim phrases as allegedly lacking positive method steps:

- “cells or cellular extracts of the microbe that have been grown *in vitro*”
- “polynucleotides of the microbe that are expressed *in vivo*.”

Claim 15 recites a positive method step of:

adsorbing a first sera sample from one or more animal model hosts infected with or previously infected with a microbe, with cells or cellular extracts of the microbe that have been grown *in vitro*.

One of skill in the art would understand the step of adsorbing a sera sample with cells or cellular extracts of the microbe that have been grown *in vitro*. The specification teaches that:

Preferably, a sample containing antibodies against antigens that are expressed by the microbe *in vivo* and *in vitro*, such as a serum sample of an infected host, are contacted with *in vitro* grown whole cells, cell extracts or both of the microbe, or whole cells, extracts of whole cells, or both of cells that are infected with the microbe of interest, *e.g.* a prokaryotic or eukaryotic cell infected with a virus or parasite.

See specification, page 12, lines 19-21 and working Example 1. Therefore, one of skill in the art, given the specification, would understand that “cells or cellular extracts of the microbe that have been grown *in vitro*” can be, *e.g.*, *in vitro* grown whole cells, cell extracts or both of the microbe, or whole cells, extracts of whole cells, or both of cells that are infected with the microbe of interest. Furthermore, the specification discusses this positive method step at, *inter alia*, page 12, line 14 through page 13, line 8 and working example 1.

Another positive method step is “probing a first expression library of the microbe with the unadsorbed antibodies from the first serum sample and isolating clones from the first expression library that bind to antibodies from the first serum sample, and probing a second expression library with the unadsorbed antibodies from the second serum sample and isolating clones from the second expression library that bind to antibodies from the second serum sample, wherein polynucleotides of the microbe that are expressed only *in vivo* are isolated for the first and second serum sample.” One of skill in the art is familiar with probing expression libraries with antibodies. Furthermore, the specification describes such procedures in detail. See page 13, line 12 through page 13, line 6, and working Example 2. Clones from the expression library that bind with unadsorbed antibodies are isolated thereby isolating a polynucleotide of the microbe that is expressed only *in vivo*. Reactive clones isolated by probing the expression library can be characterized by conventional analysis to identify a polynucleotide of a microbe that is expressed only *in vivo*. See page 14, lines 1-15 and working Example 3.

The Office asserts that “[i]f the method of independent claim 15 requires the cells or cellular extracts to be grown *in vitro* or the polynucleotide to be expressed *in vivo*, applicants are requested to provide positive method steps regarding these limitations into the claims.” As described above each of these limitations are clear such that one of skill in the art would understand what is claimed when the claims are read in light of the specification. Applicants respectfully request withdrawal of the rejection.

Double Patenting

The Office asserts that the claims 1-17 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-109 of U.S. Ser. No. 10/505,054 and claims 1-16 of U.S. Ser. No. 12/327,056. Applicants note that U.S. Ser. No. 10/505,054 is abandoned. As such the provisional rejection is moot over U.S. Ser. No. 10/505,054. The provisional rejection is not ripe as it pertains to U.S. Ser. No. 12/327,056. Applicants will respond to this rejection when/if it becomes ripe.

Conclusion

The Office asserts that the presently claimed methods are so indefinite that a meaningful search of the prior art could not be conducted. Applicants strenuously disagree with this statement. As described above the claims are indeed definite and as noted in the applicants’ reply of November 19, 2008, the claims have already been searched by the Office in an initial Office Action issued on April 18, 2008, and a Final Office Action issued on February 17, 2009. The Final Office Action had only a double patenting rejection. It is unclear how an initial Office Action and a Final Office Action could be issued in this application if the claims were too indefinite to search. The Office Action of April 18, 2008 mentioned one indefiniteness issue that was withdrawn in the February 17, 2009, Office Action. No other indefiniteness issues were raised in those Office Actions.

The claims are in condition for allowance and applicants respectfully request the issuance of a notice of allowability.

Respectfully submitted,

Dated: July 23, 2009

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